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原著論文

Stability Testing of Drug Substances Approved by the Japanese Government in 2014

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2014年に承認された医療用原薬の安定性試験について

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要　旨

2014年に日本で承認された新医療用原薬に対し、安定性試験の現状を調査した。我々は、2014年に安定性試験の記述がある66の新医療用原薬を特定した。長期保存試験としては、32原薬が25± 2 ℃/60± 5 %相対湿度（RH）または30± 2 ℃/65± 5 %RH の条件下で、14原薬が 5 ± 3 ℃で、 2 原薬が－20± 5 ℃で実施されていた。光安定性試験では、22原薬が安定で、24原薬が光不安定であり、不明のものが22原薬であった。光安定性試験で不安定であった原薬は、すべて遮光保存とされた。これらのことから、2014年に承認された新医療用原薬は、ICH ガイドラインに従って、適切に設定されていることがわかった。

キーワード

安定性試験、新医療用原薬、長期保存試験、加速試験、光安定性試験、ICH-ガイドライン

Abstract

The current status of stability testing in Japan was investigated. We identified 66 new drug substances that had undergone stability testing in 2014. Among these, there were 32 were tested at 25±2℃/60±5% relative humidity（RH）or 30±2℃/65±5%RH, 14 were tested at 5±3℃, and 2 were tested at －20±5℃ in long-term testing. In the photostability testing, 22 new drug substances were found to be stable optically and 24 were unstable optically. New drug substances that appeared unstable in photostability testing were stored in darkness. From these results, the new drug substances approved according to the ICH guidelines in Japan in 2014 were found to perform adequately.

Key words

stability testing, new drug substance, long-term testing, accelerated testing, photostability testing, guideline

Introduction

Stability test results are an essential requirement for New Drug Application. The requirement is discussed in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[1] Revisions of the guidelines on stability testing have been performed several times.

The guidelines for stability testing of new drug substances are listed for Table 1.

ICH–Q1A (R2) says that the stability data package for new drug substances or drug products is sufficient for a registration application within the three regions of the European Union, Japan, and the United States.[1]

ICH–Q1B says that the intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that light exposure does not cause unacceptable changes.[2]

ICH–Q1C is an annex to the ICH–Q1A (R2) and provides recommendations on what should be submitted regarding stability of new dosage forms by the original applicant, after the original submission for a new drug substance or product.[3]

ICH–Q1D provides recommendations on the application of bracketing and matrixing to stability studies.[4]

ICH–Q1E provides recommendations on how to use stability data generated in accordance with the principles detailed in the ICH–Q1A (R2) that can be used to propose retest periods or a shelf life in a registration application.[5] Additionally, this guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or shelf life for a drug product that extends beyond the period covered by "available data from the stability studies under long-term storage condition".[5]

In New Drug Application, long term studies and acceleration studies must be included in the stability testing according to the ICH–Q1A (R2).

Presently, we analyzed data on the stability testing of 66 drug substances that were approved in Japan in 2014 and verified whether these ICH guidelines were applied adequately. Previously, we reported such analyses in new drug products,[7] but this report is first one regarding new drug substances.

MATERIALS AND METHODS

Drugs that were approved from January to December 2014 were surveyed. The information sources were the data summaries (Module 2 of Common Technical Document (CTD) in the present system) that were submitted by the applicants for New Drug Appli-

Table 1 The guidelines for stability testing for new drug substances

Name of Guideline	Abbreviation
Stability Testing of New Drug Substances and Products	ICH–Q1A (R2)
Stability Testing: Photostability Testing of New Drug Substances and Products,	ICH–Q1B
Stability Testing for New Dosage Form	ICH–Q1C
Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	ICH–Q1D
Evaluation of Stability Data,	ICH–Q1E

cations and the approval documents that described specifications and test methods of drug substances. This information, especially the quality section, is not all publicly available, although Module 2 of the CTD and review reports available on the internet.[6] Therefore, we did not disclose the individual substances' name.

RESULTS AND DISCUSSION

Classification of Approved Drugs by Stability Testing

There were 131 new drugs that were approved from January to December 2014, excluding antiseptics for medical devices, *in vivo* diagnostics, and generic drugs.

At first, we classified the drugs as those that underwent stability testing and those that did not. The 131 new drugs consisted of 66 drugs that did undergo stability testing and 65 that did not (Fig. 1).

Because 66 bulk drugs for which the stability test was not carried out were drugs with new administration routes or drugs with new indications or new dosage and administration, which is the so-called approval matter partial change application, they were not imposed on stability test. Therefore, they do not have a description of a stability test.

We investigated further details of the 66 new drug substances as shown in the following sections.

Long-term Testing and Accelerated Testing

According to ICH-Q1A (R2),[1] long-term testing for general new drug substances is performed at 25±2℃/60±5% relative humidity (RH) or 30±2℃/65±5%RH. Accelerated testing for general new drug substances is performed at 40±2℃/75±5%RH. In the case of drug substances intended for storage in a refrigerator, long-term testing is performed at 5±3℃, and accelerated testing is performed at 25±2℃/60±5%RH. In the case of drug substances intended for storage in a freezer, long-term testing is performed at −20±5℃.

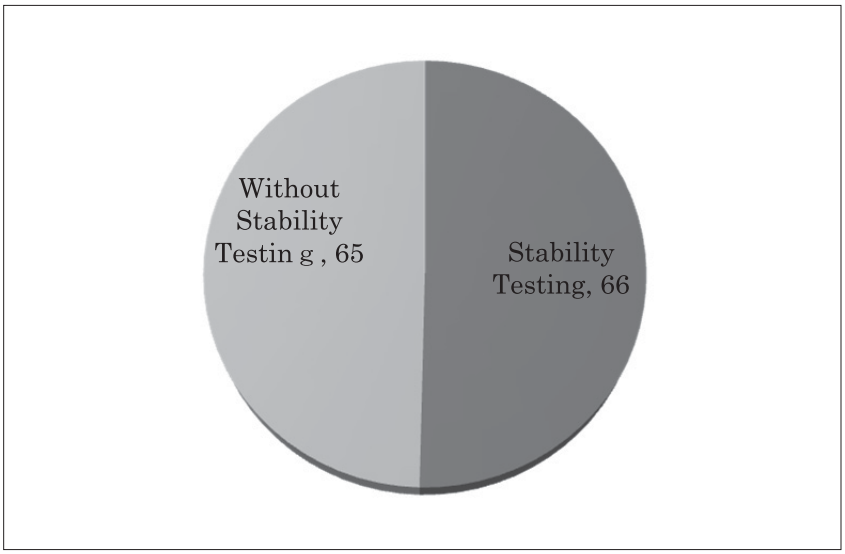

Fig. 1 Classification of New Drug Substances according to whether or not they underwent stability testing

Additionally, long term-testing for drug substances intended for storage at −20℃ is treated on a case-by-case basis.

Long-term testing was performed for 32 new drug substances at 25±2℃/60±5%RH or 30±2℃/65±5%RH, for 14 at 5±3℃, for 2 at −20±5℃, for 8 at other temperatures, and 10 for unknown temperatures (Fig. 2).

Among these new drug substances, 20 had shelf life or re-test period of >36 months, 1 had shelf life or re-test period of 30 months, 19 had shelf life or re-test periods of 24 months, 5 had shelf life or re-test period of 18 months, 1 had shelf life or re-test period of 15 months, 5 had shelf life or re-test period of 12 months, 1 had shelf life or re-test period of 6 months, and 14 had shelf life or re-test period that was unknown (Fig. 3).

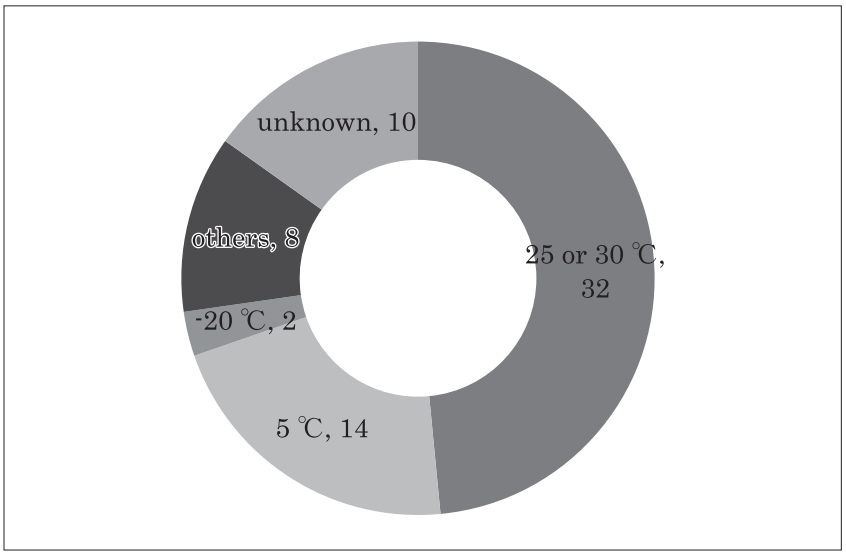

Fig. 2 Specifications of storage temperatures used in long term testing

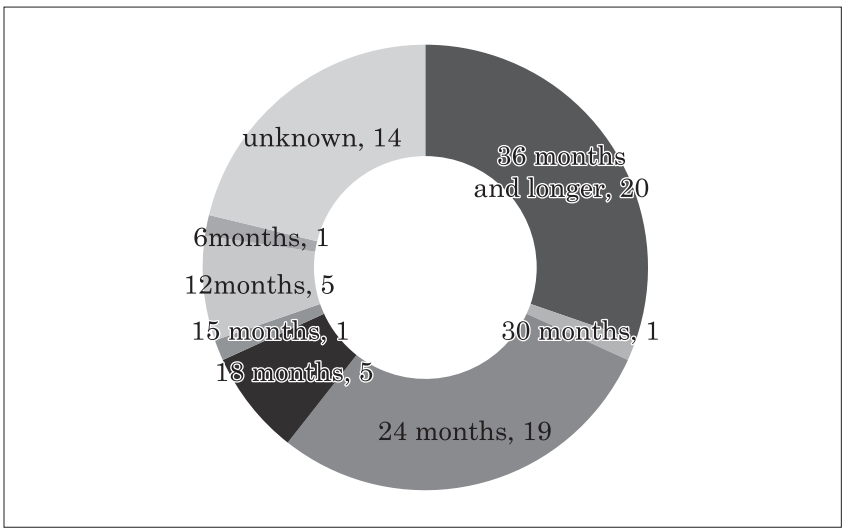

Fig. 3 Specifications according to shelf life or re-test period

There were 17 new drug substances that applied ICH–Q1E[5] and postponed the expiration date (Fig. 4).

Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed under the accelerated condition. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data. As for Q1E application items, a long-term testing of 12–24 months was carried out, thus we think that shelf life or re-test period of new drug substances are set adequately.

Accelerated testing was performed for all new drug substances (data not shown).

From results of a long- term testing and accelerated testing, we think that shelf life or re-test period of new drug substances are set adequately.

Photostability Testing

According to ICH–Q1B,[2] photostability testing consists of two parts for drug substances: forced degradation testing and confirmatory testing. The purpose of forced degradation testing is to evaluate the overall photostability of the material for methods development purposes and/or degradation pathway elucidation. In these forced degradation studies, a variety of exposure conditions are used. Decomposition products are sometimes observed that are unlikely to be formed under the conditions used for confirmatory studies under forcing conditions. This information is useful in developing and validating analytical methods. On the other hand, confirmatory studies are conducted to provide the information necessary for packaging and labeling.

Twenty-two new drug substances were stable optically and 24 were unstable optically (Fig. 5). New drug substances that appeared unstable in photostability testing were stored in darkness. Thus, we believe the storage conditions are appropriate.

In conclusion, our review described 66 new drug substances approved in Japan in 2014 that were based on ICH guidelines, all of

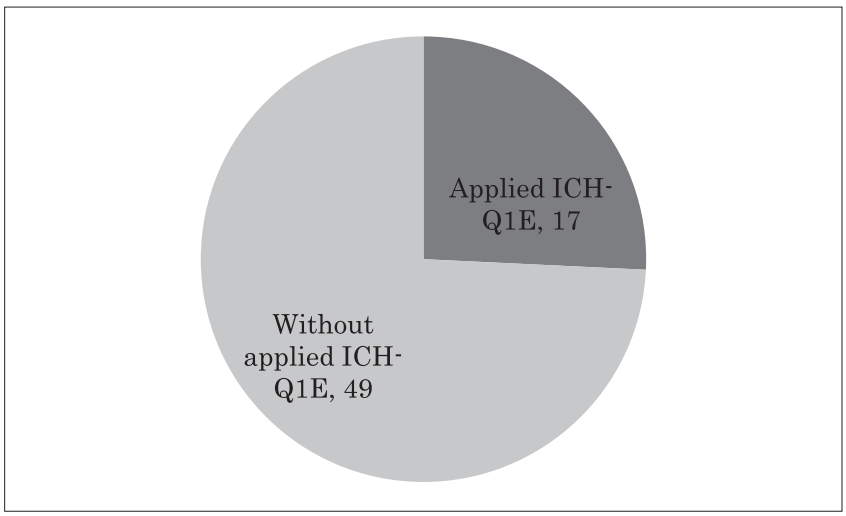

Fig. 4 The number of ICH–Q1E applications

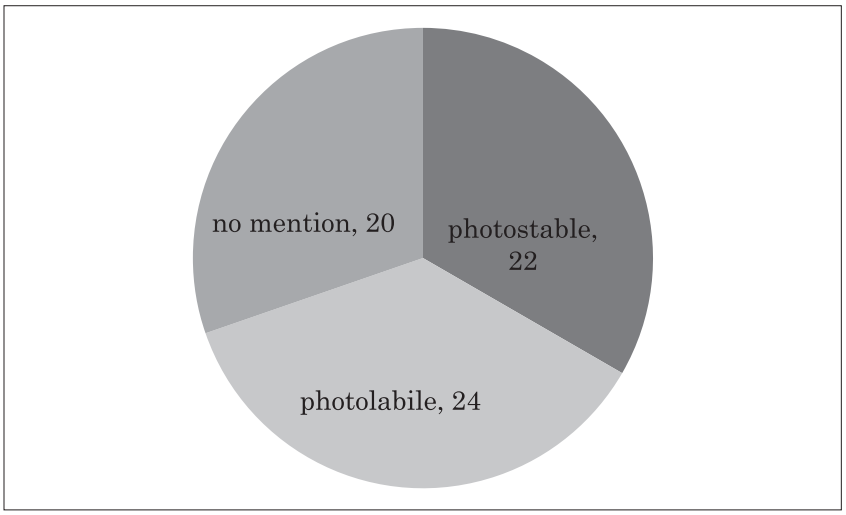

Fig. 5 Itemization of photostability testing

which performed adequately.

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Conflict of Interest

The authors declare no conflict of interest.

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